Dimethoate Metabolism (85-1) and dermal absorption (85-2) studies

Primary Reviewer: Paul Chin, Ph.D.
Section 2, Toxicology Branch I (7509C)
Secondary Reviewer: Joycelyn Stewart, Ph.D.
Section Head, Section 2, Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Metabolism - Rat; OPPTS 870.7485 [§85-1]
Dermal Absorption

DP BARCODE: D228188 SUBMISSION CODE: S508343
P.C. CODE: 035001 TOX. CHEM. NO.: 358

TEST MATERIAL (PURITY): Dimethoate (nonradiolabled purity = 99.1%; radiolabled purity = >98%)

SYNONYMS: O,O-dimethyl-S-(N-methylcarbamoylmethyl) phosphorodithioate; Dimethogen; Trimetion

CITATION:
D. Kirkpatrick; 1995; ^{14}C-Dimethoate: The Biokinetics and metabolism in the rat. Volumes 1 and 2; Huntingdon Life Sciences Ltd., Cambridgeshire, England; Dec. 18, 1995; DTF 16: MRID 43964001

SPONSOR: The Dimethoate Task Force

EXECUTIVE SUMMARY:

Groups of male and female Wistar rats were dosed with ^{14}C-dimethoate (labeled in the O-methyl groups) at a single oral dose (10 or 100 mg/kg), an intravenous dose (10 mg/kg) or 14-day repeated oral doses of dimethoate at 10 mg/kg followed by a single oral dose of ^{14}C-dimethoate at 10 mg/kg. Dimethoate was rapidly absorbed, metabolized, and eliminated in rats for all dosing regimens. There were no remarkable sex-, dose- or treatment-related differences in the absorption, distribution, and elimination of dimethoate in rats. Total recovery of radioactivity ranged between 91% and 97% of the administered dose for all tested groups within 5 days after dosing. The excretion of radioactivity into urine was rapid and most of the radioactivity was excreted in the urine (85-91% of the dose) of the animals. A small amount of radioactivity was found in feces (1-2% of the dose), in the tissues and remaining carcass (1-2%), and in the expired air as carbon dioxide (2-3%). ^{14}C-concentration in all tissues was less than 7 ppm after single oral dose at 100 mg/kg and less than 0.3 ppm after a single or multiple oral doses at 10 mg/kg (14-daily dose) and an intravenous dose at 10 mg/kg.

Most (83-91%) of the administered dose in urine samples from orally or intravenously dosed rats were identified by HPLC analysis followed by confirmation by mass spectrometry. Four metabolites identified were Ref II (Omethoate, 1-6% of dose), Ref XVI (Dimethylthiophosphoric acid, 4-11% of dose), Ref XV (Dimethyldithiophosphate, 20-30% of dose), and Ref III

(Dimethoate carboxylic acid, 29-46% of dose). There were no qualitative or quantitative differences in the metabolite profiles for dose level and sex of rats after oral or intravenous administration of ^{14}C-dimethoate. Five radioactive components were not identified but no component in the urine samples represented more than 7% of the dose. Unchanged parent in the urine samples represented 0.4-2% of the dose. The metabolic pathway consisted of hydrolytic and oxidative pathways. The hydrolytic pathway (major) involves cleavage of the C-N bond to yield dimethoate carboxylic acid that was subsequently metabolized to dimethyldithiophosphate, dimethylthiophosphoric acid and dimethylphosphoric acid. The minor metabolic pathway involves oxidation of dimethoate to its oxon analogue, omethoate, that was subsequently metabolized to dimethylthiophosphoric acid and dimethylphosphoric acid. Loss of the methoxy groups of the parent to yield carbon dioxide is a minor metabolic pathway.

Dermal absorption was 7.6-8.2%, 7.9-8.5%, and 9-11% of the administered dose from rats 1, 2, and 5 days after dermal treatment at 10 mg/kg, respectively. Dermal absorption was 1-2% of the dose from rats 1, 2, or 5 days after dermal treatment at 100 mg/kg. Dermal absorption was approximately 1 mg/kg in terms of weight equivalent of dimethoate absorbed at each dose level. The amounts of metabolites identified in the urine of the dermally dosed rats represented 1.4-1.5% and 5.4-6% (consisted of Ref XV and Ref V) of the administered dose following dermal administration of 100 or 10 mg/kg, respectively. Biliary excretion of radioactivity by bile-cannulated rats accounted for 4-5% of the dose 2 days after a single oral administration of ^{14}C-dimethoate at 10 or 100 mg/kg.

Classification: Core-acceptable This study satisfies the guideline requirement for a metabolism study (85-1) in rat.

A. MATERIALS:

1. Test compound:

	Unlabeled test material	Radiolabeled test material
Description	Crystalline solid	Not provided
Purity	99.1%	>98%
Specific activity	Not applicable	14.55 MCi/g
Position of radiolabel	Not applicable	^{14}C was labeled in the O-methyl groups (see position of label below)

The structure and radiolabel position of dimethoate are shown below:

* denotes position of radiolabel

2. Vehicle: Water for oral doses; isotonic saline for intravenous doses; aqueous sodium carboxymethylcellulose solution for dermal treatments, 1% (w/v).

3. Test animals: Species: Rat; Sex: Male and female; Strain: Wistar; Age at administration of radioactive dose: 7-10 weeks; Mean body weight: 195-224 g; Source: Charles River UK Ltd, Kent, UK; Acclimation period: 5 days.

4. Preparation of dosing solutions: ^{14}C-Dose solutions were prepared immediately before dosing.

B. STUDY DESIGN:

The study was designed to study the pharmacokinetics of ^{14}C-dimethoate in rats following oral gavage (high and low), intravenous, 14-day repeated oral doses, and dermal administration. The test group and dose level used in the study are shown below.

Dimethoate Metabolism (85-1) and dermal absorption (85-2) studies

Experiment	Route of administration (Dose level: mg/kg)	Experiment type	No. rats /group		Time of collection of excreta, blood, and tissues
			M	F	
2b 2c 2d	oral (100) oral (10) oral, repeated (a) (10)	excretion/balance	5	5	Excreta at 6, 12, 24h, and daily up to 5 days; expired air at 6 and 24h, and daily up to 3 days; tissues at 5d.
2e 2g 2h	i.v.(10) dermal (10) dermal (100)	excretion/balance	5	5	Samples were taken as described above 2b.
3a 3b	oral (100) oral (10)	kinetics of radioactivity in plasma	5	5	Group 1--1, 6, 48, 120h; group 2--0.25, 2, 12, 72, 144h; group 3--0.5, 4, 24, 96, 168h
3c	oral (100)	kinetics of plasma parent compound	12	12	0.5, 2, 6, 24h
4a 4b	oral (100) oral (10)	biliary excretion	3	3	Bile at 3h, 6h, 12h, 24, 48h
5a	oral (10)	whole body autoradiography	5	5	One of each sex at 0.5, 2, 6, 48, 120h
5b 5c 5d	oral (100) oral (10) oral, repeated (10)	tissue distribution	9	9	Tissue (3/sex) at 0.5, 2, 48h

Source: Study Report DTF 16. Quantities of radioactivity administered to rats ranged from 2.93 to 6.19 x 10^7 dpm (extracted from Appendix 8).
(a) daily gavage treatments for 14 days with unlabeled dimethoate at 10 mg/kg followed by a single dose of labeled dimethoatea at 10 mg/kg on day 15. Experiments 1a/b, 2a, and 2f are pretest or pilot experiments and they are not included in the above table.

C. TREATMENT OF ANIMALS and ANALYSIS OF EXCRETA & TISSUES

Dose levels of 10 and 100 mg/kg were selected for oral administration based on the results of the pre-test experiments (1a and 1b) using non-radiolabeled dimethoate. In the pre-test experiments, oral administration of dimethoate at 100 and 10 mg/kg produced slight toxic effects (body tremors) and no observable toxic effects, respectively.

No toxic effects were observed at dermal administration of 250 mg/kg. Dose levels of 10 and 100 mg/kg were selected for dermal administration to facilitate the comparison of results obtained after oral and dermal administration.

1. Oral ^{14}C-dose administration

   Rats were subjected to oral doses (10 or 100 mg/kg) of ^{14}C-dimethoate or daily gavage treatments for 14 days with unlabeled dimethoate at 10 mg/kg followed by a single dose of labeled dimethoate at 10 mg/kg on day 15.

2. Intravenous ^{14}C-dose administration

   For intravenous dosing, animals were dosed via a tail vein at a rate of 5 ml/kg body weight.

3. Dermal ^{14}C-dose administration

   About 24 hours before to application, an area on the back of each rat was shaved using electric clippers. The dose formulation was applied at a rate of 1 ml/kg/body weight over an area of 10 cm^2 and the treated area was protected with a plastic net cover attached by adhesive dressing to prevent loss and disturbance. The cover was not in contact with the treated area. At 6 hours after dosing, the cover was removed and the treated area was washed with cotton wool swabs soaked in soapy water. The animals were transferred to glass metabolism cages until sacrifice at 120 hours. Urine and feces were collected at 6-24 and then at 24-hour intervals.

4. Bile duct-cannulated rats experiment

The operation was carried out with animals under halothane-oxygen anethesia. The bile duct was cannulated with polythene tubing and the incision in the animal was closed with sutures. Animals were dosed following recovery from the anesthetic.

5. Analysis of excreta and tissues

   Urine and feces were collected at the times indicated in the Study Design. Blood was removed from the heart by cardiac puncture after halothane anesthesia at the times showed in the Study Design. All rats were killed by cervical dislocation at the times specified in the Study Design. The stomach, gastrointestinal tract, adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, pancreas, spleen, testes, thyroid gland, uterus, muscle, fat, bone, bone marrow and skin and the remaining carcass were removed from those animals shown. Samples were analyzed for radioactivity by tissue combustion and/or liquid scintillation counting.

D. STATISTICS

The statistics employed for this study were limited to calculations of mean values.

E. QUALITY ASSURANCE

A signed statement of compliance with Good Laboratory Practices (GLP) and a signed statement of Quality Assurance (QA) were included in the submission.

F. RESULTS

Excretion

The excretion of radioactivity into urine and feces was rapid and complete in all groups tested. Table 1 shows the comparison of recovery of radioactivity in rats 5 days after a single oral (high and low), repeated, or intravenous administration of ^{14}C-dimethoate. Total recovery of radioactivity ranged between 91% and 97% of the administered dose for all tested groups within 5 days after dosing. The major route of excretion of radioactivity was via the urine (85-91% of the dose). Small amounts of radioactivity were found in feces (1-2% of the dose), in the tissues and remaining carcass (1-2%), and in the expired air as carbon dioxide (2-3%). No marked sex-related difference was observed in the excretion of administered radioactivity.

Table 2 shows the comparison of recovery of radioactivity in rats 5 days after a dermal administration of ^{14}C-dimethoate at 10 or 100 mg/kg. Dermal absorption (based on a total amount of radioactivity recovered from urine, tissues, and feces) was 9-11% and 1.2-1.6% of the administered dose from rats treated at 10 and 100 mg/kg, respectively. Dermal absorption was 7.6-8.2% and 7.9-8.5% of the administered dose from rats 1 and 2 days after dermal treatment at 10 mg/kg, respectively. Dermal absorption was 1-2% of the dose from rats 1 or 2 days after dermal treatment at 100 mg/kg. Dermal absorption was approximately 1 mg/kg in terms of weight equivalent of dimethoate absorbed at each dose level. No marked sex-related difference was observed in the absorption patterns. The amount of radioactivity recovered from skin wash, extracts from dressing, and treated skin was 62-84%, 1.4-3.6%, and 2-17% of the administered, respectively. Total recovery of radioactivity ranged between 89% and 93% of the administered dose for all tested groups within 5 days after dosing.

Bile cannulation study

Table 3 shows the comparison of recovery of radioactivity in bile-cannulated rats 2 days after a single oral administration of ^{14}C-dimethoate at 10 or 100 mg/kg. The majority of radioactivity was found in urine (82-87% of the administered dose) and a small amount of radioactivity was found in bile (3.7-4.5% of the administered dose), feces (1.4-3.3%), and tissues (2.1-3%). Total recovery of radioactivity ranged between 91% and 96% of the administered dose for all tested groups within 2 days after dosing.

Pharmacokinetics

Pharmacokinetics parameters in rats after a single oral administration of ^{14}C-dimethoate are shown in Table 4. Tmax (time to reach peak plasma ^{14}C-concentration) was 0.25-0.5 hours after oral dosing at 10 or 100 mg/kg. Cmax (mean peak plasma ^{14}C-concentration) was 51-93 and 7.7-8.6 mg equivalents/l in rats dosed at 100 and 10 mg/kg, respectively. Mean areas under the

curves (AUC) were 417-687 and 42-59 mg equivalents hr/l in rats dosed at 100 and 10 mg/kg, respectively. After oral dosing of ^{14}C-dimethoate, the plasma elimination of dimethoate was biphasic. The terminal half-life (t 1/2) values were 36-46 and 42-59 hours for the 100 and 10 mg/kg groups, respectively. Concentrations of unchanged dimethoate in plasma in rats 0.5 hours after oral administration at 100 mg/kg ranged 6-7 mg/l. The concentration fell to 1-2 mg/l at 2 and 6 hours after administration (not shown in Table).

Tissue concentration at 0.5, 2, and 48 hours (Experiments 5b-5d)

Tissue ^{14}C-concentration at 0.5, 2, and 48 hours after single oral (10 or 100 mg/kg) or 7-day repeated oral administrations (10 mg/kg) of ^{14}C-dimethoate (Experiments 5b-5d, Table not shown) are as follows:

Single oral dose, 10 mg/kg

No marked sex-related difference was observed in the tissue distribution of administered radioactivity. Tissue ^{14}C-concentration in almost all tissues was highest 0.5 hours after dosing. At 48 hours after oral administration of 10 mg/kg, tissue ^{14}C-concentration (expressed as ppm equivalent/tissue) in all tissues found in both sexes were less than 1 ppm. Tissue ^{14}C-concentration found in both sexes were highest in liver (0.3% of the dose) and gastrointestinal tract with contents (0.2-0.7% of the dose).

Multiple oral dose, 10 mg/kg (7-daily dose)

No marked sex-related difference was observed in the tissue distribution of administered radioactivity. Tissue ^{14}C-concentration in almost all tissues was highest 0.5 hours after dosing in females and 0.5 and 2 hours after dosing in males. At 48 hours after oral administration of 10 mg/kg, tissue ^{14}C-concentration (expressed as ppm equivalent/tissue) in all tissues found in both sexes were less than 3 ppm. Tissue ^{14}C-concentration (expressed as ppm) found in both sexes were highest (approximately 3 ppm) in liver and pancreas.

Single oral dose, 100 mg/kg

No marked sex-related difference was observed in the tissue distribution of administered radioactivity. Tissue ^{14}C-concentration in almost all tissues was highest 0.5 hours after dosing in females and 0.5 and 2 hours after dosing in males. At 48 hours after oral administration of 100 mg/kg, tissue ^{14}C-concentration (expressed as ppm equivalent/tissue) in all tissues found in both sexes were less than 8 ppm. Tissue ^{14}C-concentration (expressed as ppm) found in both sexes were highest (4-8 ppm) in the liver and pancreas.

Tissue distribution at 120 hours (Experiments 2b-2d)

Tissue ^{14}C-concentration in animals at 120 hours after oral administration of an oral (single or 14-day repeated dosing), intravenous, or dermal doses are as follows (Tables 5 and 6):

Single oral dose, 10 mg/kg

No marked sex-related difference was observed in the tissue distribution of administered radioactivity. Tissue ^{14}C-concentration (expressed as ppm equivalent/tissue) in all tissues found in rats were less than 0.3 ppm. Tissue ^{14}C-concentration found in both sexes were highest in the liver, kidney, and pancreas.

Multiple oral dose, 10 mg/kg (14-daily dose)

No marked sex-related difference was observed in the tissue distribution of administered radioactivity. Tissue ^{14}C-concentration (expressed as ppm equivalent/tissue) in all tissues found in rats was less than 0.3 ppm and they were generally slightly higher (up to two-fold) than single oral dose group. Repeated dosing of rats at 10 mg/kg for 14 days did not alter the pattern of excretion of orally administered ^{14}C-dimethoate at 10 mg/kg.

Single oral dose, 100 mg/kg

No marked sex-related difference was observed in the tissue distribution of administered radioactivity. Tissue ^{14}C-concentration (expressed as ppm equivalent/tissue) in all tissues found in rats was less than 7 ppm. Tissue ^{14}C-concentration (expressed as ppm) were highest in the pancreas (5-7 ppm) in both sexes and the thyroid (2-5 ppm) of males.

Intravenous dose, 10 mg/kg

Tissue ^{14}C-concentration (expressed as ppm equivalent/tissue) in all tissues were similar to those of the low-dose single oral dose group described above.

Dermal dose, 10 and 100 mg/kg

Tissue ^{14}C-concentration (expressed as ppm equivalent/tissue) in all tissues found were less than 0.2 ppm for 10 mg/kg group and less than 0.9 ppm for 100 mg/kg group. Often, the tissue concentration was less than the limit of detection.

Whole-Body Autoradiobiography

The results of whole-body autoradiography of rats (one animal/sex/time) sacrificed at 0.5, 2, 6, 48, and 120 hours after a single oral dose at 10 mg/kg corroborated those of the quantitative experiments reported above. The greatest amount of radioactivity was associated with the contents of the gastrointestinal tract, the liver, and kidneys.

Identification of Metabolites

Table 7 shows the results of HPLC analysis of 48 hour urine samples following single oral, intravenous or dermal doses. Analysis of the urine samples showed nine ^{14}C containing HPLC peaks and parent (dimethoate). Most (83-91%) of the administered dose in the urine samples from orally or intravenously dosed rats were identified. There were no qualitative or quantitative differences in the metabolite profiles for dose level and sex of rats after oral or intravenous administration of ^{14}C-dimethoate. Four metabolites identified by co-chromatography with the authentic reference standards were Ref II (Omethoate), Ref XVI (Dimethylthiophosphoric acid), Ref XV (Dimethyldithiophosphate), and Ref. III (Dimethoate carboxylic acid). The identities of

the three metabolites, Ref XVI, Ref XV, and Ref III, were confirmed by mass spectrometry.

Two major metabolites (Ref XV, 20-30% of the dose and Ref III, 29-46%) accounted for most of the administered doses. The amount of two other metabolites (Ref II, 1.3-5.6% of dose and Ref XVI, 4.0-10.8%) represented minor quantity. Five radioactive components (U1, U2a, U3, U5, and U6) were not identified but no component in the urine samples represented more than 7% of the administered dose. Unchanged parent in the urine samples represented 0.4-2% of the administered dose.

At least 13 radioactive components were found in bile samples from animals dosed at 10 or 100 mg/kg (not shown in Table). The major metabolites were Ref III (1-2% of dose) and Ref XV (0.2-0.4% of dose). Unchanged parent in bile samples represented 0.1-0.2% of the dose.

Incubation of the urine or bile samples with beta-glucuronidase/sulphatase did not change the chromatographic profiles of these samples, showing that glucuronic acid or sulphate conjugation of the metabolites did not occur.

The amounts of metabolites identified in the urine of the dermally dosed rats represented 1.4-1.5% and 5.4-6% of the administered dose following dermal administration of 100 or 10 mg/kg, respectively. HPLC analysis of plasma samples obtained at 6 hours after dosing (the kinetics study of parent in plasma, Experiment 3c, single oral, 100 mg/kg) showed 2 metabolites (Ref III and Ref XV, 2-4 ppm), dimethoate (1-2 ppm) and 6 unidentified metabolites (0.1-3 ppm). TLC analysis of kidney samples obtained at 7 days after dosing (the tissue distribution study, Experiment 5b-5d, single oral, 10 and 100 mg/kg and repeated oral, 10 mg/kg) showed 3 identified metabolites (Ref III, Ref XV, and Ref XVI representing 0.2-0.8% of the dose), dimethoate (0.04-0.34% of the dose) and 7 unidentified metabolites.

TLC analysis of liver samples obtained at 7 days after dosing (the tissue distribution, Experiment 5b-5d, single oral at 10 and 100 mg/kg and repeated oral at 10 mg/kg) showed 2 identified metabolites (Ref XV and Ref XVI representing 0.35-0.95% of the dose), dimethoate (0.06-0.154% of the dose) and 6 unidentified metabolites.

A proposed metabolic pathway for dimethoate in the rat is shown in Figure 1. The authors provided this metabolic pathway that is consistent with the available data. The metabolic pathway consisted of hydrolytic (major) and oxidative (minor) pathways. The hydrolytic pathway involves cleavage of the C-N bond to yield dimethoate carboxylic acid (III) that was subsequently metabolized to dimethyldithiophosphate (XV), dimethylthiophosphoric acid (XVI) and dimethylphosphoric acid (XVII). The minor metabolic pathway involves oxidation of dimethoate to its oxon analogue, omethoate, that was subsequently metabolized to Ref XVI and XVII. Loss of the methoxy groups of the parent to yield carbon dioxide is a minor metabolic pathway.

G. DISCUSSION

Groups of male and female Wistar rats were dosed with ^{14}C-dimethoate (labeled in the O-methyl groups) at a single oral dose (10 or 100 mg/kg), an intravenous dose (10 mg/kg) or 14-day repeated oral doses of dimethoate at 10 mg/kg followed by a single oral dose of ^{14}C-dimethoate at 10 mg/kg. Dimethoate was rapidly absorbed, metabolized, and eliminated in rats for all dosing regimens. There were no remarkable sex-, dose- or treatment-related differences in the absorption, distribution, and elimination of dimethoate in rats. Total recovery of radioactivity

ranged between 91% and 97% of the administered dose for all tested groups within 5 days after dosing. The excretion of radioactivity into urine was rapid and most of the radioactivity was excreted in the urine (85-91% of the dose) of the animals. A small amount of radioactivity was found in feces (1-2% of the dose), in the tissues and remaining carcass (1-2%), and in the expired air as carbon dioxide (2-3%). ^{14}C-concentration in all tissues was less than 7 ppm after single oral dose at 100 mg/kg and less than 0.3 ppm after single or multiple oral dose at 10 mg/kg (14-daily dose) and intravenous dose at 10 mg/kg.

Most (83-91%) of the administered dose in urine samples from orally or intravenously dosed rats were identified by HPLC analysis followed by confirmation by mass spectrometry. Four metabolites identified were Ref II (Omethoate, 1-6% of dose), Ref XVI (Dimethylthiophosphoric acid, 4-11% of dose), Ref XV (Dimethyldithiophosphate, 20-30% of dose), and Ref III (Dimethoate carboxylic acid, 29-46% of dose). There were no qualitative or quantitative differences in the metabolite profiles for dose level and sex of rats after oral or intravenous administration of ^{14}C-dimethoate. Five radioactive components were not identified but no component in the urine samples represented more than 7% of the dose. Unchanged parent in the urine samples represented 0.4-2% of the dose. The metabolic pathway consisted of hydrolytic and oxidative pathways. The hydrolytic pathway (major) involves cleavage of the C-N bond to yield dimethoate carboxylic acid that was subsequently metabolized to dimethyldithiophosphate, dimethylthiophosphoric acid and dimethylphosphoric acid. The minor metabolic pathway involves oxidation of dimethoate to its oxon analogue, omethoate, that was subsequently metabolized to dimethylthiophosphoric acid and dimethylphosphoric acid. Loss of the methoxy groups of the parent to yield carbon dioxide is a minor metabolic pathway.
Dermal absorption was 7.6-8.2%, 7.9-8.5%, and 9-11% of the administered dose from rats 1, 2, and 5 days after dermal treatment at 10 mg/kg, respectively. Dermal absorption was 1-2% of the dose from rats 1, 2, or 5 days after dermal treatment at 100 mg/kg. Dermal absorption was approximately 1 mg/kg in terms of weight equivalent of dimethoate absorbed at each dose level. The amounts of metabolites identified in the urine of the dermally dosed rats represented 1.4-1.5% and 5.4-6% of the administered dose following dermal administration of 100 or 10 mg/kg, respectively. Biliary excretion of radioactivity by bile-cannulated rats accounted for 4-5% of the dose 2 days after a single oral administration of ^{14}C-dimethoate at 10 or 100 mg/kg.

C:\wp51\dimethoa\43964001.der 9/16/96

Table 1. The comparison of recovery of radioactivity in rats 5 days after a single oral, repeated, or intravenous administration of ^{14}C-dimethoate (mean values in percentage of radioactivity administered)

Expe-riment	Dose level (mg/kg)	Urine and cage wash (1)	Expired air (2)	Feces (3)	Total (4) = (1+2+3)	Total tissues (5)	TOTAL RECOVERY (6) = (4+5)
2b, %	100, oral	90.8	2.44	1.45	94.7	1.14	95.9
2b, &	100, oral	90.8	2.53	1.45	94.8	1.88	96.6
2c, %	10, oral	91.3	2.10	1.15	94.6	0.67	95.3
2c, &	10, oral	85.4	2.17	1.56	89.1	1.45	90.6
2d, %	10, oral repeated	90.6	2.07	1.30	94.0	1.04	95.0
2d, &	10, oral repeated	88.9	2.28	1.22	92.4	1.72	94.1
2e, %	10, i.v.	88.9	1.76	1.15	91.8	0.81	92.6
2e, &	10, i.v.	89.4	1.62	1.35	92.4	0.96	93.3

Source: Tables 3a-4a, Study Report DTF 16

Table 2. The comparison of recovery of radioactivity in rats 5 days after a dermal administration of ^{14}C-dimethoate (mean values in percentage of radioactivity administered)

Expe-riment	Dose level (mg/kg)	Urine and cage wash (1)	Total tissues (2)	Feces (3)	Total absorbed (4) = (1+2+3)	Skin wash (6 hours) (5)	Extracts from Dressing (6)	Treated skin (7)	TOTAL RECOVERY (8) = (4+5+6+7)
2g, %	10	8.27	0.76	0.21	9.19	62.5	3.42	17.3	92.5
2g, &	10	9.26	0.76	0.58	10.6	62.1	3.16	13.3	89.1
2h, %	100	1.13	0.11	0.05	1.18	84.1	1.35	3.65	90.2
2h, &	100	1.32	0.22	0.13	1.64	83.7	3.64	2.18	91.1

Source: Tables 5a, Study Report DTF 16

Table 3. The comparison of recovery of radioactivity in bile-cannulated rats 2 days after a single oral administration of ^{14}C-dimethoate (mean values in percentage of radioactivity administered)

Expe-riment	Dose level (mg/kg)	Urine and cage wash (1)	Total Bile (2)	Feces (3)	Total tissues (4)	TOTAL RECOVERY (5) = (1+2+3+4)
4a, %	100	82.8	4.05	1.40	3.00	91.3
4a, &	100	81.6	3.68	3.31	2.28	90.8
4b, %	10	82.6	4.07	2.39	2.77	91.8
4b, &	10	87.0	4.52	2.69	2.07	96.3

Source: Tables 7a, Study Report DTF 16

Table 4. Pharmacokinetics parameters in rats after a single oral administration of ^{14}C-dimethoate

Expe-riment	Dose level (mg/kg)	Cmax (mg equiv./l)	Tmax (hours)	AUC (mg equiv. hr/l)	Terminal half-life (hours) (a)
4a, %	100	50.7	0.25	417.0	36.1
4a, &	100	93.2	0.5	686.6	46.4
4b, %	10	8.62	0.5	49.4	42.0
4b, &	10	7.68	0.5	48.9	59.3

Source: Table 10, Study Report DTF 16
Cmax = peak plasma radioacivity concentration
Tmax = time to reach peak plasma radioactivity concentration
AUC = area under the curve
a: calculated using the 12-168 hours data

Table 5. Tissue Distribution of Radioactivity at 5 Days Following an Oral Administration of ^{14}C-dimethoate to Rats.

	Mg Dimethoate Equivalents/kg (PPM) found					
	10 mg/kg		10 mg/kg (a)		100 mg/kg	
	%	&	%	&	%	&
Adrenal	0.11	0.12	0.20	0.24	2.03	2.01
Bone	0.07	0.07	0.05	0.05	0.41	0.37
Bone marrow	0.07	0.10	0.20	0.16	2.97	1.64
Brain	0.04	0.05	0.06	0.07	0.41	0.50
Fat	0.06	0.08	0.03	0.04	0.72	0.48
Heart	0.08	0.10	0.11	0.13	0.83	1.07
Intentines & contents	0.04	0.07	0.07	0.10	0.47	0.70
Kidneys	0.15	0.19	0.26	0.26	1.60	1.75
Liver	0.24	0.28	0.34	0.34	2.16	2.11
Lungs	0.10	0.14	0.15	0.17	0.91	1.19
Muscle	0.06	0.07	0.08	0.08	0.65	0.68
Ovaries	-	0.08	-	0.14	-	1.03
Pancreas	0.19	0.26	0.19	0.37	5.15	6.63
Skin	0.09	0.11	0.11	0.44	0.77	0.82
Spleen	0.08	0.10	0.14	0.16	0.87	1.17
Stomach & contents	0.03	0.09	0.14	0.14	0.30	0.49
Testes	0.06	-	0.10	-	0.63	-
Thyroid	<0.14	0.13	0.18	0.23	5.18	1.99
Uterus	-	0.11	-	0.12	-	0.76
Whole blood	0.06	0.09	0.11	0.14	0.36	0.52
Plasma	0.03	0.04	0.06	0.07	0.36	0.52

Sources: Table 20, Study Report DTF 16
a: Rats received a single oral 10 mg/kg non-radiolabeled dose once daily for 14 consecutive days before administration of the radioactive dose.

Table 6. Tissue Distribution of Radioactivity at 5 Days Following an Intravenous and Dermal Administration of ^{14}C-dimethoate to Rats.

	Mg Dimethoate Equivalents/kg (PPM) found					
	Intravenous, 10 mg/kg		Dermal, 10 mg/kg		Dermal, 100 mg/kg	
	%	&	%	&	%	&
Adrenal	0.11	0.11	<0.09	<0.03	<0.31	<0.16
Bone	0.03	0.02	<0.02	0.02	<0.10	<0.10
Bone marrow	0.06	0.07	<0.05	<0.07	<0.59	<0.63
Brain	0.03	0.03	<0.01	0.01	<0.06	0.06
Fat	0.04	0.03	<0.02	<0.02	<0.09	<0.01
Heart	0.06	0.07	<0.01	<0.01	<0.07	<0.08
Intentines & contents	0.03	0.07	0.01	0.03	<0.07	0.13
Kidneys	0.13	0.13	0.01	0.02	<0.07	<0.07
Liver	0.20	0.20	0.02	0.03	<0.07	0.08
Lungs	0.08	0.09	0.01	0.02	<0.07	<0.07
Muscle	0.05	0.05	0.01	0.02	<0.05	<0.05
Ovaries	-	0.07	-	<0.02	-	<0.01
Pancreas	0.17	0.29	0.02	0.03	<0.07	0.08
Skin	0.07	0.06	0.02	0.12	0.20	0.30
Spleen	0.06	0.07	<0.02	<0.02	<0.08	<0.09
Stomach & contents	0.03	0.07	<0.02	0.04	<0.08	<0.08
Testes	0.05	-	<0.01	-	<0.05	-
Thyroid	<0.12	<0.01	<0.15	<0.14	<0.88	<0.74
Uterus	-	0.06	-	<0.02	-	<0.12
Whole blood	0.06	0.07	0.01	0.01	<0.03	<0.03
Plasma	0.03	0.04	0.01	0.01	<0.02	<0.02

Sources: Table 21, Study Report DTF 16

Table 7. Results of HPLC analysis of 48 hour urine samples following single oral, intravenous or dermal doses

	Expressed as percent of administered dose as metabolite											
	Oral 10 mg/kg		Oral 10 mg/kg (a)		Oral 100 mg/kg		Intravenous 10 mg/kg		Dermal 10 mg/kg		Dermal 100 mg/kg	
	%	&	%	&	%	&	%	&	%	&	%	&
U1	5.2	5.0	6.5	6.0	4.8	3.8	4.3	3.9	- (c)	-	-	-
Ref II (Omethoate)	1.5	2.5	3.2	5.6	3.7	3.7	1.3	1.8	-	-	-	-
U2a	0.3	0.2	0.3	0.3	0.4	0.3	(b)	(b)	-	-	-	-
U3	4.1	4.0	4.2	3.6	2.2	2.0	3.7	3.7	-	-	-	-
Ref XVI (Dimethylthiophosphoric acid)	8.3	5.7	10.8	7.3	8.7	4.7	6.5	4.0	-	-	-	-
U5	0.9	0.7	1.2	1.2	1.0	1.3	0.9	0.7	-	-	-	-
U6	2.5	2.1	2.1	1.5	2.3	1.9	3.7	1.8	-	-	-	-
Ref XV (Dimethyldithiophosphate)	26.6	25.2	29.7	27.4	20.3	22.1	22.5	24.1	2.9	3.2	-	-
Dimethoate	1.4	0.7	0.9	0.6	0.7	2.0	0.4	0.5	-	-	-	-
Ref III (Dimethoate carboxylic acid)	37.8	35.1	29.1	31.0	43.2	44.4	42.7	45.7	2.5	2.8	-	-
Others	2.3	1.9	2.2	2.1	2.3	2.7	1.7	1.7	-	-	-	-
TOTAL **(% of dose identified)**	90.9	83.1	90.2	86.6	89.6	88.9	87.7	87.9	5.4	6.0	1.4	1.5

Sources: Table 23 of the Study Report DTF 16; Results are expressed as percent of administered dose as metabolite
a: Rats received a single oral 10 mg/kg non-radiolabeled dose once daily for 14 consecutive days before administration of the radioactive dose.
b: included in 'others' c: - indicates less than 1% of the dose

Figure 1. Proposed metabolic pathway of dimethoate in rats
(Taken from DIAGRAM, p.13 of Study Report DTF 16)